

RESEARCH ARTICLE

Challenges in Collating Spirometry Reference Data for South-Asian Children: An Observational Study

Sooky Lum^{1*}, Vassiliki Bountziouka¹, Philip Quanjer², Samatha Sonnappa^{1,3}, Angela Wade⁴, Caroline Beardsmore⁵, Sunil K. Chhabra⁶, Rajesh K. Chudasama⁷, Derek G. Cook⁸, Seeromanie Harding⁹, Claudia E. Kuehni¹⁰, K. V. V. Prasad¹¹, Peter H. Whincup⁸, Simon Lee¹, Janet Stocks¹



OPEN ACCESS

Citation: Lum S, Bountziouka V, Quanjer P, Sonnappa S, Wade A, Beardsmore C, et al. (2016) Challenges in Collating Spirometry Reference Data for South-Asian Children: An Observational Study. PLoS ONE 11(4): e0154336. doi:10.1371/journal.pone.0154336

Editor: Philipp Latzin, University Children's Hospital Bern, SWITZERLAND

Received: December 23, 2015

Accepted: April 11, 2016

Published: April 27, 2016

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Data Availability Statement: All data are available from the following URL: <http://discovery.ucl.ac.uk/1473451/>.

Funding: This work was supported by the Wellcome Trust [WT094129MA (SLum); 068362/Z/02/Z(PHW)], Asthma UK [10/013(JS); 07/048(CEK)], Indian Council of Medical Research(SS), The Swiss National Science Foundation (CEK) [32003B-122341; 32003B_144068, PZ00P3_147987/1, PDFMP3-123162] and the Medical Research Council (SH) [MC_U130015185/MC_UU_12017/1]. The SLIC study team acknowledges the support of the National

1 Respiratory, Critical Care & Anaesthesia section (Portex Unit), UCL, Institute of Child Health, London, United Kingdom, **2** Department of Pulmonary Diseases and Department of Paediatrics-Pulmonary Diseases, Erasmus Medical Centre, Erasmus University, Rotterdam, Netherlands, **3** Department of Paediatric Pulmonology, Rainbow Children's Hospital, Bangalore, India, **4** Clinical Epidemiology, Nutrition and Biostatistics section, UCL, Institute of Child Health, London, United Kingdom, **5** Institute for Lung Health, NIHR Leicester Respiratory Biomedical Research Unit, and Department of Infection, Immunity & Inflammation, University of Leicester, Leicester, United Kingdom, **6** Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India, **7** Community Medicine Department, PDU Medical College, Rajkot, Gujarat, India, **8** Population Health Research Institute, St George's, University of London, London, United Kingdom, **9** Diabetes & Nutritional Sciences Division, Kings College London, London, United Kingdom, **10** Institute of Social and Preventative Medicine, University of Bern, Switzerland, **11** Department of Physiology, Vemana Yoga Research Institute, Hyderabad, India

* s.lum@ucl.ac.uk

Abstract

Availability of sophisticated statistical modelling for developing robust reference equations has improved interpretation of lung function results. In 2012, the Global Lung function Initiative (GLI) published the first global all-age, multi-ethnic reference equations for spirometry but these lacked equations for those originating from the Indian subcontinent (South-Asians). The aims of this study were to assess the extent to which existing GLI-ethnic adjustments might fit South-Asian paediatric spirometry data, assess any similarities and discrepancies between South-Asian datasets and explore the feasibility of deriving a suitable South-Asian GLI-adjustment.

Methods

Spirometry datasets from South-Asian children were collated from four centres in India and five within the UK. Records with transcription errors, missing values for height or spirometry, and implausible values were excluded (n = 110).

Results

Following exclusions, cross-sectional data were available from 8,124 children (56.3% male; 5–17 years). When compared with GLI-predicted values from White Europeans, forced expired volume in 1s (FEV₁) and forced vital capacity (FVC) in South-Asian children were on average 15% lower, ranging from 4–19% between centres. By contrast, proportional

Institute for Health Research (NIHR), through the Comprehensive Clinical Research Network and the NIHR Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

reductions in FEV₁ and FVC within all but two datasets meant that the FEV₁/FVC ratio remained independent of ethnicity. The 'GLI-Other' equation fitted data from North India reasonably well while 'GLI-Black' equations provided a better approximation for South-Asian data than the 'GLI-White' equation. However, marked discrepancies in the mean lung function z-scores between centres especially when examined according to socio-economic conditions precluded derivation of a single South-Asian GLI-adjustment.

Conclusion

Until improved and more robust prediction equations can be derived, we recommend the use of 'GLI-Black' equations for interpreting most South-Asian data, although 'GLI-Other' may be more appropriate for North Indian data. Prospective data collection using standardised protocols to explore potential sources of variation due to socio-economic circumstances, secular changes in growth/predictors of lung function and ethnicities within the South-Asian classification are urgently required.

Introduction

Lung function tests are an integral part of clinical management of respiratory disease but reliable interpretation of results relies on availability of suitable reference data to help distinguish the effects of disease from those of growth and development. Appropriate reference equations are therefore crucial both in clinical management and for interpretation of clinical trials in which lung function is a primary outcome[1,2]. In addition to the major determinants of height, age and sex, lung function is also influenced by ethnicity.[3,4] Some studies have suggested that these differences may be primarily attributed to social deprivation[5,6]. However, while there is evidence that severe deprivation may impact negatively on both growth and lung function,[7,8] recent studies in developed countries have shown that the contribution of socio-economic factors is minimal[9–13] and that ethnic differences in lung function persist even when such factors are taken into account.

Since publication of the most recent ERS/ATS guidelines for spirometry in 2005 [14] there have only been two publications on spirometry reference ranges for Indian adults.[15,16] By contrast, of the various publications reporting spirometry reference equations for children from the Indian sub-continent (hereafter referred to as South-Asian), seven have been published in the past 15 years. [8,17–22] These have, however, been derived using simple regression techniques based on data collected in different parts of the Indian subcontinent, using different equipment in children of different age ranges and socio-economic backgrounds and may therefore not be generalisable.

Development of sophisticated statistical modelling techniques for deriving more robust reference equations has provided opportunities to improve interpretation of lung function results across the age span, with the GLI publishing the first global all-age, multi-ethnic reference equations for spirometry in 2012[3]. These equations were available for 5 distinct ethnic groups, i.e. Caucasian (hereafter referred to as "White"), African-American (hereafter referred to as "Black"), North-East Asian (e.g. North China, Korea), South-East Asian (e.g. South China, Thailand, Taiwan) and Other (consisting of groups other than the 4 main groups and those of mixed ethnic origin). Although some spirometry data South-Asians were provided to the GLI team, results from these studies were sufficiently disparate with respect both to mean

results and their distribution to preclude the necessary combination of datasets to derive reliable reference equations [3]. The lack of a 'normal range' for South-Asian children currently limits the application and interpretation of their lung function tests.

Two recent studies of 5–12 year old South-Asian school children in London, UK and in Bangalore, India using identical equipment, protocol and quality control (QC) [7,23] showed that after adjusting for height, age and sex [3], average forced expired volume in 1 second (FEV_1) and forced vital capacity (FVC) were very similar in Indian urban children residing in Bangalore city to those living in the UK; both being approximately 11% ($\sim 0.9z$ -score) lower than that predicted for White European children [7], with no ethnic differences in the FEV_1 /FVC ratio. The similarity of results from these two studies, suggested that it should be possible to derive an additional GLI-adjustment (coefficient) suitable for use in South-Asian children. The primary aim of this study was to assess the extent to which existing GLI-ethnic adjustments might fit South-Asian paediatric spirometry data. The secondary aim was to assess any similarities and discrepancies between South-Asian datasets and the feasibility of deriving a suitable GLI-adjustment if needed for interpreting such data. Some results from this study have been reported in abstract form [24].

Materials and Methods

UK centres who had recently (last 15 years) published or collected spirometry data from healthy South-Asian subjects aged 5–18 years or Indian centres who had either submitted such data to the GLI team or recently published their findings were invited to collaborate. See supporting information in [S1 File](#), Section 1.1 for recruitment and exclusion criteria and [S1 Table](#) for further details. All centres indicating willingness to participate were requested to provide information on population characteristics (e.g. age, sex, anthropometry, ethnicity, socio-economic circumstances (SEC)) and equipment used. Data were anonymised before submission to this collaboration and came from research studies for which full local ethics approvals were obtained, i.e. from the M.S. Ramaiah Medical College and Teaching Hospitals Ethics Board, Bangalore; Vallabhnbhai Patel Chest Institutional Ethics Committee, Delhi; Ethical Committee of the Government Medical College, Surat, Gujarat; Ethical Committee of the National Institute of Nutrition, Hyderabad; Multicentre Research Ethics Committee, UK (for CHASE and DASH study); Leicestershire Research Ethics Committee (for the two Leicester studies) and Research Ethics Committee: London-Hampstead: REC 10/H0720/53 (SLIC study). Parental written consent and verbal assent from each child were obtained prior to assessments.

Data

Among the 11 centres (six UK and five Indian centres) contacted, ten centres responded positively although only nine were able to submit the requested data within the available time frame. Datasets ($n = 8413$ initially) were available from four centres in India (Bangalore, Delhi, Hyderabad and Gujarat) [7,17,18,21,25] and five in the UK (three in London and two in Leicester; [Table 1](#)) [10,11,23,26–28]. Records with transcription errors that could not be resolved, with missing values for height, FEV_1 or FVC, or where lung function values were deemed implausible (i.e. FEV_1 /FVC ratio > 1.0 ; FEV_1 or FVC $\leq 0.3L$) were discarded ($n = 110$).

Data management and statistical analysis

Results are presented as mean(SD) for continuous variables or as frequencies(%) for categorical variables. Anthropometry was expressed as sex-specific z-scores based on Indian growth charts derived from well-nourished children [29]. Only three studies were able to provide spirometric flow-volume curves for retrospective quality check on data provided ([Table 1](#)). To ascertain

Table 1. Summary of studies included in the collation of South-Asian data.

Centre	Publication (author, year)	Region where data collection performed	Date of collection	Number of healthy subjects	Ethnicity (based on ancestral origin#)	Age range (year)	Birth data (Y/N)	Sitting height (Y/N)	SEC	Spirometer used	Data available for QC? (Y/N)
A	Sonnappa, 2015[7]	Bangalore, India	2013	782	100% Indian	5.0–16.4	N	Y	Y	Easy-on-PC, ndd	Y
B	Chhabra, 2012[17]	Delhi, India	2007–10	670	100% Indian	6–17	N	N	N	Medisoft Micro 5000	Y
C	Doctor TH, 2010[18]	South Gujarat, India	2007–08	648	100% Indian	8.0–13.9	N	N	N	Spirolab II, MIR 010	N
D	Raju, 2003 [25]; Raju, 2004[21]	Hyderabad, India	1995–97	2540	100% Indian	5–15	N	Y	Y	Vitalograph	N
E	Barone-Adesi, 2015 [28]	London, Birmingham, Leicester, UK (CHASE study)	2004–07	1547	32% Indian; 23% Bangladeshi; 37% Pakistani; 8% SA Other	9.0–11.1	N	Y	Y	Vitalograph compact 2	N
F	Whitrow, 2008[11]	London, UK (DASH study)	2001–02	1064	46% Indian; 18% Bangladeshi; 36% Pakistani	11.2–13.9	N	Y	Y	Micro Plus, MicroMedical	N
G	Whittaker, 2005[26]	Leicester city, UK	2001–02	177	Not specified	6.5–11.5	Y	Y	Y	Jaeger Masterscope	N
H	Stripolli, 2013 [10]	Leicester, UK (LRC)	2006–10	210	Not specified	8.6–14.1	Y	N	Y	Pneumotrac, Vitalograph	N
I	Lum, 2015[9]	London, UK (SLIC study)	2011–13	486	68% Indian; 11% Bangladeshi; 8% Pakistani; 13% Sri Lankan /mixed SA	5.3–11.5	Y	Y	Y	Easy-on-PC, ndd	Y

Abbreviations: SA: South-Asian; SEC: Socio-economic circumstances; Y: Yes; N: No; QC: Quality control—Y indicates that data were readily available for independent inspection and over-read of flow-volume curves; SLIC: “Size and Lung function In Children”; CHASE: “Child Heart And health Study in England”; DASH: “Determinants of Adolescent Social wellbeing and Health”; LRC: Leicester Respiratory Cohort”. # Ancestral origin determined via parental questionnaire.

doi:10.1371/journal.pone.0154336.t001

overall distribution of data from each study, FEV₁, FVC, and FEV₁/FVC were initially expressed as z-scores using the GLI-2012 equations for White subjects as a baseline[3].

Within each centre, lung function results were then inspected to ascertain i) the relationship between the lung function z-scores against age and height to ensure that there were no trends in residuals (see S1 File, section 1.2 for details)[3] ii) the spread of data between-subjects iii) whether offsets in FEV₁ and FVC relative to the ‘GLI-White’ equation were proportional, as had been observed in over 60 datasets previously submitted to the GLI-2012[30]. After assessing the South-Asian spirometry data in relation to White subjects, the exercise was repeated to assess the fit of existing GLI-ethnic adjustments [3]. The appropriateness of any given reference equation to specific datasets was also ascertained by checking the percentage of healthy subjects within each centre with results falling at or below the 5th centile (i.e. 5% lower limit of normal (LLN) ≤ -1.645 z-scores).

Similarities and discrepancies between datasets, including the potential impact of SEC in Indian-based studies, were examined. Prior to deriving any new South-Asian GLI-adjustment factors (S1 File, Section 1.2.1), datasets with non-proportional reductions in FEV₁ and FVC,

were excluded and the remaining data were analysed both before and after removing additional datasets that were visibly discrepant from others with respect to either mean offset or between-subject variability.

Analyses were performed using IBM SPSS Statistics version 22 (IBM Corp. Armonk, NY). One-way ANOVA was performed to compare the lung function indices (z-scores based on GLI-White) between centres. Post-hoc pairwise comparisons were subsequently performed using the Tukey's honestly significant difference test which takes into account sample size when calculating the 95% Confidence Intervals (CI).

Results

Data for analysis were available from 8,124 children (56.3% male; age range 5–17 years), the majority of whom were of Indian origin (Tables 1 and 2).

Anthropometry

Based on the Indian growth charts[29], after adjusting for sex and age, South-Asian children residing in the UK were significantly taller and heavier (by 0.56z-scores and 0.84z-scores respectively) than those living in India (S2 Table). While anthropometry was similar between UK centres, mean values from Indian centres ranged from -0.63 to +0.49z-scores for height and -0.97 to +0.29z-scores for weight (Table 2), children from Northern India (Delhi-centre B) being tallest and heaviest.

Spirometry

Lung function results are summarised in Table 2. When compared with GLI-predicted values from White Europeans, FEV₁ in South-Asian children were on average 15% lower, ranging from 4–19% (-0.37 to -1.57 z-scores) according to centre, with an excessive proportion of healthy children (i.e. >>5%) falling below the lower limit of normal (LLN) as defined by the 5th centile. Similar results were found for FVC (average 16% lower; range 6–23%), with Centre B (Delhi) and Centre G (Leicester) having significantly larger FEV₁ and FVC than those from all other centres ($p < 0.01$) except Centre I, in whom zFVC was similar to that in Centre G ($p = 0.93$). However, proportional reductions in FEV₁ and FVC within all but two datasets (D and G) meant that FEV₁/FVC generally remained independent of ethnicity[3]. The distributions of z-scores according to centre are shown in the Fig 1, illustrating the wide scatter of data from some centres. When data were limited to only those from India (i.e. excluding Pakistani, Bangladeshi, Sri Lankan and Other/mixed South-Asian), results were similar to those observed from all data.

Associations between extreme poverty and lung function

Among the UK studies, lung function differences were not explained by socio-economic factors[9–11]. By contrast, the association between SEC and lung function among children living in India is clearly illustrated in data from Bangalore(A) where both anthropometry and lung volumes were significantly lower in those living in rural areas or exposed to poorer SEC (Table 3)[7]. Anthropometry and lung function were also higher in those from high SEC compared to those from medium or low SEC in the Hyderabad(D) dataset, although the distinction between the latter groups was less clear. Details of SEC were not available from the remaining two India-based studies (B and C).

Table 2. Group characteristics and spirometry results (based on GLI-White equations) according to centre.

Centre	A	B	C	D	E	F	G	H	I	Total
Country	India (Bangalore)	India (Delhi)	India (Gujarat)	India (Hyderabad)	UK (CHASE)	UK (DASH)	UK (Leicester)	UK (LRC)	UK (SLIC)	
Subjects, n	782	670	648	2540	1547	1064	177	210	486	8124
Boys (%)	57%	55%	62%	61%	49%	61%	40%	52%	48%	56%
Age (y)	9.9(2.2)	11.6(3.3)	10.7(1.3)	10.0(3.1)	9.9 (0.4)	12.6(0.6)	9.0 (1.4)	11.8 (1.1)	8.3(1.6)	10.4 (2.5)
zHeight#[29]	-0.60(1.15)	0.49 (1.02)	0.13(1.21)	-0.63(1.00)	0.18(1.02)	0.20 (1.03)	0.18(1.02)	0.20 (1.00)	0.31 (0.99)	-0.11 (1.13)
zWeight#[29]	-0.62(1.18)	0.29 (0.97)	-0.06(1.06)	-0.97(0.82)	0.27(1.05)	0.23 (1.01)	0.19(1.01)	0.24 (1.07)	0.16 (0.97)	-0.24 (1.13)
zFEV ₁ (GLI-W)	-1.26(0.90)	-0.67 (0.87)	-1.57(0.90)	-1.56(1.08)	-1.15 (1.18)	-1.21 (1.04)	-0.37(0.94)	-1.13 (1.04)	-0.91 (0.86)	-1.26 (1.08)
FEV ₁ (%pred, GLI-W)	85.0 (10.7)	92.1 (10.1)	81.6 (10.6)	81.0 (13.5)	86.6 (13.8)	85.7 (12.3)	95.7 (11.1)	86.8 (12.3)	89.0 (10.4)	85.0 (13.0)
zFVC (GLI-W)	-1.19(0.95)	-0.54 (0.90)	-1.65(0.97)	-1.96(1.08)	-1.13 (1.24)	-1.07 (1.61)	-0.67(0.93)	-1.28 (1.00)	-0.81 (0.86)	-1.36 (1.24)
FVC (% pred, GLI-W)	86.0 (11.1)	93.7 (10.7)	80.9 (11.3)	76.7 (13.0)	87.0 (14.3)	87.8 (18.9)	92.1 (11.1)	85.2 (11.4)	90.3 (10.4)	84.1 (14.7)
zFEV ₁ /FVC (GLI-W)	-0.14(0.86)	-0.23 (0.95)	0.15(0.86)	0.98(0.98)	0.06(1.28)	0.12 (1.63)	0.66(0.98)	0.29 (1.04)	-0.22 (0.92)	0.32 (1.22)
Proportion of children with lung function ≤ -1.64 z-scores (i.e. $\leq 5^{\text{th}}$ centile) according to the GLI-White equations, n (%) ^a										
zFEV ₁ (GLI-W)	36.2%	13.3%	47.5%	45.9%	32.1%	31.5%	6.2%	30.5%	19.8%	35.0%
zFVC (GLI-W)	31.3%	10.6%	51.2%	61.1%	32.2%	38.2%	13.6%	32.9%	16.0%	40.3%
zFEV ₁ /FVC (GLI-W)	3.2%	5.4%	2.9%	1.2%	9.1%	14.6%	1.1%	3.8%	6.6%	5.5%

Data presented as Mean(SD) unless otherwise specified. #According to Khadiilkar growth reference; Abbreviation: z: z-score (i.e. standard deviation score) %pred: percent predicted; GLI-W: GLI reference equations based on White European subjects.

^aIf the reference equations are appropriate, 5% of a healthy population would be expected to fall at or below the 5th centile (lower limit of normal).

doi:10.1371/journal.pone.0154336.t002

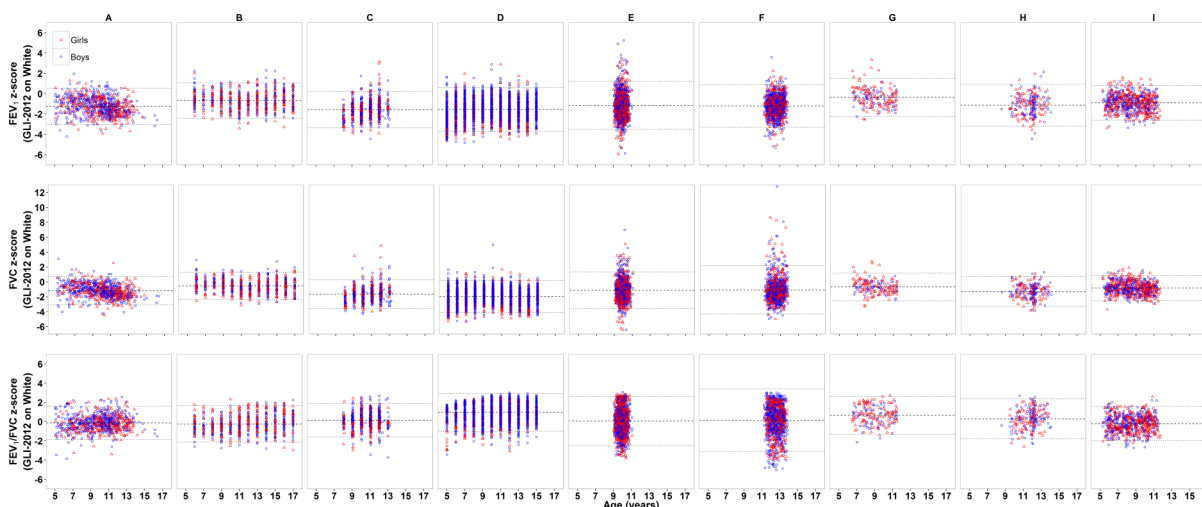


Fig 1. Distribution of lung function data (based on GLI-White) vs. age according to centre. Symbols: Blue denotes data from boys and Red denotes data from girls. Dashed line = mean value and dotted lines 95% limits of agreement (Mean \pm 2 SD) for each dataset. Centres: A = Bangalore; B = Delhi; C = Gujarat; D = Hyderabad; E = CHASE (London); F = DASH (London); G = Leicester City; H = LRC (Leicester); I = SLIC (London). Note the different scales used on the y-axis reflecting the greater spread of FVC than FEV₁ data. Note: Age was only recorded to the nearest year for data from Centres B, C and D.

doi:10.1371/journal.pone.0154336.g001

Table 3. Association between extreme poverty and lung function in children residing in India.

Centre	A ₁	A ₂	A ₃	D ₁	D ₂	D ₃
Country	Bangalore (urban)	Bangalore(semi-urban)	Bangalore (rural)	Hyderabad(high SEC)	Hyderabad (medium SEC)	Hyderabad(low SEC)
Subjects, n	383	234	165	1002	1018	529
Boys (%)	68%	43%	50%	50%	52%	100%
Age (y)	9.0 (1.9)	11.3 (2.0)	10.0 (2.0)	10.2 (3.1)	9.8 (3.0)	10.0 (3.2)
zHeight#	0.06 (0.90)	-1.19 (1.00)	-1.30 (0.98)	-0.29 (0.92)	-0.83 (0.93)	-0.92 (1.07)
zWeight#	0.13 (0.93)	-1.28(0.92)	-1.43 (0.91)	-0.65 (0.80)	-1.13 (0.77)	-1.29 (0.75)
zFEV ₁ (GLI-W)	-0.93 (0.85)	-1.46 (0.77)	-1.75 (0.88)	-1.30 (1.05)	-1.76 (1.09)	-1.69 (1.08)
zFVC (GLI-W)	-0.86 (0.86)	-1.40 (0.79)	-1.67 (1.05)	-1.73 (1.02)	-2.14 (1.12)	-2.09 (1.08)
zFEV ₁ /FVC (GLI-W)	-0.16 (0.80)	-0.19 (0.75)	-0.06 (1.10)	1.02 (0.93)	0.94 (1.02)	0.95 (0.98)

Data presented as Mean(SD) unless otherwise specified; #According to Khadilkar growth reference[29]; Abbreviation: SEC: socio-economic circumstance; GLI-W: according to GLI-White equations[3]. Although confident of the FEV₁ data, authors of the Hyderabad study suspected that the relatively low and non-proportional change in FVC and hence the elevated FEV₁/FVC may have been due to difficulties in children achieving a full forced expiration in this field study.

doi:10.1371/journal.pone.0154336.t003

Extent to which existing GLI-ethnic adjustments might fit South-Asian data

The extent to which the existing GLI-South-East Asian equations (derived from subjects from South China, Thailand and Taiwan, who are geographically closest to those originating from the Indian subcontinent) fitted the South-Asian data is summarised in Table 4. While relative offsets for zFEV₁ and zFVC were smaller than when compared with GLI-White equations, the GLI-South-East Asian equations provided a poorer fit for zFEV₁/FVC, and an excessive proportion of healthy children had results that fell below the 5th centile for all outcomes. While the

Table 4. Spirometry data from South-Asian subjects according to GLI-South-East Asian reference.

Centre	A	B	C	D	E	F	G	H	I	Total
n	782	670	648	2540	1547	1064	177	210	486	8124
zFEV ₁ (GLI-SEA)	-0.47 (0.95)	0.17(0.93)	-0.80 (0.97)	-0.81 (1.15)	-0.31 (1.26)	-0.42 (1.12)	0.53 (1.02)	-0.30 (1.12)	-0.09 (0.93)	-0.46 (1.15)
zFVC (GLI-SEA)	-0.16 (1.02)	0.56(0.97)	-0.65 (1.07)	-1.02 (1.16)	-0.05 (1.34)	-0.01 (1.76)	0.44 (1.02)	-0.22 (1.08)	0.26(0.94)	-0.33 (1.35)
zFEV ₁ /FVC (GLI-SEA)	-0.64 (0.90)	-0.72 (1.00)	-0.33 (0.91)	0.53(1.02)	-0.43 (1.33)	-0.35 (1.72)	0.18 (1.01)	-0.18 (1.10)	-0.72 (0.95)	-0.15 (1.28)
Proportion of children with lung function below the 5th centile according to the GLI-South-East Asian equations^a (%)										
zFEV ₁ (GLI-SEA)	10.5%	2.1%	17.3%	22.6%	12.1%	13.3%	1.1%	10.0%	3.9%	14.2%
zFVC (GLI-SEA)	6.3%	0.6%	16.2%	28.2%	8.1%	11.2%	1.1%	8.6%	1.2%	14.1%
zFEV ₁ /FVC (GLI-SEA)	10.7%	17.6%	7.3%	3.0%	17.2%	19.7%	5.1%	10.5%	17.5%	11.3%

Data presented as Mean (SD) unless otherwise specified. Centres A = Bangalore; B = Delhi; C = Gujarat; D = Hyderabad; E = CHASE (London); F = DASH (London); G = Leicester City; H = LRC (Leicester); I = SLIC (London)

^aIf the reference equations are appropriate, 5% of a healthy population would be expected to fall at or below the 5th centile (LLN). When data from Centres D and G were excluded (non-proportional reduction in FEV₁ and FVC), group mean(SD) for zFEV₁ was -0.33(1.12) z-scores; zFVC: -0.03(1.32) and zFEV₁/FVC: -0.48(1.26), while proportion of children with lung function below the 5th centile according to GLI-SE Asian equations were 10.7%, 7.9% and 15.4% respectively.

doi:10.1371/journal.pone.0154336.t004

Table 5. Spirometry data from South-Asian subjects according to GLI-Black reference.

Centre	A	B	C	D	E	F	G	H	I	Total
n	782	670	648	2540	1547	1064	177	210	486	8124
zFEV ₁ (GLI-B)	-0.06 (0.96)	0.57 (0.93)	-0.36 (0.96)	-0.39(1.17)	0.09 (1.27)	0.01 (1.11)	0.89 (1.0)	0.10 (1.11)	0.29 (0.92)	-0.05 (1.16)
zFVC (GLI-B)	0.08 (1.00)	0.78 (0.97)	-0.38 (1.04)	-0.75 (1.17)	0.17 (1.33)	0.25 (1.72)	0.61 (0.97)	0.01 (1.06)	0.46 (0.91)	-0.08 (1.33)
zFEV ₁ /FVC (GLI-B)	-0.25 (0.87)	-0.34 (0.96)	0.04 (0.87)	0.88 (0.99)	-0.05 (1.29)	0.02 (1.65)	0.56 (0.99)	0.19 (1.06)	-0.33 (0.92)	0.22(1.23)
Proportion of children with lung function below the 5th centile according to the GLI-Black equations^a (%)										
zFEV ₁ (GLI-B)	4.0%	0.7%	7.4%	13.8%	6.0%	6.7%	0	5.2%	1.1%	7.6%
zFVC (GLI-B)	3.7%	0.3%	9.4%	21.4%	5.9%	7.3%	1.1%	6.2%	0.4%	10.1%
zFEV ₁ /FVC (GLI-B)	3.8%	7.5%	3.5%	1.5%	10.9%	15.2%	1.1%	4.3%	7.8%	6.4%

Data presented as Mean (SD) unless otherwise specified. Centres A = Bangalore; B = Delhi; C = Gujarat; D = Hyderabad; E = CHASE (London); F = DASH (London); G = Leicester City; H = LRC (Leicester); I = SLIC (London)

^aIf the reference equations are appropriate, 5% of a healthy population would be expected to fall at or below the 5th centile (LLN). When data from Centres D and G were excluded (non-proportional reduction in FEV₁ and FVC), group mean(SD) for zFEV₁ was 0.08 (1.11) z-scores; zFVC: 0.20 (1.30) and zFEV₁/FVC: -0.11 (1.21), while proportion of children with lung function below the 5th centile according to GLI-Black equations were 4.9%, 5.1% and 8.9% respectively.

doi:10.1371/journal.pone.0154336.t005

entire South-Asian dataset fitted the predicted values for Black-African origin subjects (15% lower than White subjects) reasonably well (Table 5), marked differences in relative mean offsets and distribution of results (SD of z-scores >>1.0) between the various South-Asian datasets were still observed.

Although not appropriate for most of the centres, application of the ‘GLI-Other’ reference appeared to fit data from Centre B (northern South-Asian) relatively well, with mean (SD) for both FEV₁ and FVC approximating 0 (1), albeit with a slight negative offset for FEV₁/FVC (Table 6). Under such circumstances, use of an adjusted LLN to reflect the actual 5th centile for FEV₁/FVC in that dataset (Table 7; see also S1 File, section 2.1.1) could avoid over-diagnosing abnormalities. Similarly, although the ‘Other’ equation fitted FVC data from centre G, non-proportional differences in FEV₁ and FVC meant that there would be considerable under-estimation of airway disease unless an adjusted LLN to reflect the 5th centile was applied to data from this centre (Table 7).

This exercise was not repeated for the GLI-North-East Asian prediction equations since on average these are only 3% lower than GLI-White, and would therefore under-estimate lung function for all South-Asian data.

Derivation of new GLI-adjustments for South-Asian children

The marked discrepancies in the mean lung function z-scores between centres (Table 2) especially when examined according to SEC (Table 3), meant that not only did none of the existing GLI-equations fit data from all of the individual centres, but precluded derivation of a single South-Asian GLI-adjustment. As data from Centres D and G had non-proportional differences in FEV₁ and FVC (Table 2; Tables 4–6), these data were excluded from subsequent attempts to derive new South-Asian GLI-adjustments. Data with similar mean offsets were collated before modelling the data as described in the S1 File. The selection of datasets for inclusion within different models were based on the i) significantly higher anthropometric (Table 2) and spirometric indices in children from north India compared to other centres (Model 1) ii) potential

Table 6. Spirometry data from South-Asian subjects according to GLI-Other reference.

Centre	A	B	C	D	E	F	G	H	I	Total
n	782	670	648	2540	1547	1064	177	210	486	8124
zFEV ₁ (GLI-O)	-0.73 (0.96)	-0.10 (0.93)	-1.05 (0.96)	-1.05 (1.16)	-0.59 (1.27)	-0.67 (1.11)	0.23(1.00)	-0.58 (1.11)	-0.36 (0.92)	-0.72 (1.15)
zFVC (GLI-O)	-0.59 (1.06)	0.15(1.02)	-1.10 (1.10)	-1.47 (1.23)	-0.50 (1.40)	-0.44 (1.83)	-0.01 (1.04)	-0.68 (1.13)	-0.17 (0.97)	-0.77 (1.41)
zFEV ₁ /FVC (GLI-O)	-0.33 (0.90)	-0.42 (1.00)	-0.02 (0.91)	0.85(1.03)	-0.12 (1.34)	-0.04 (1.72)	0.50(1.02)	0.13(1.10)	-0.41 (0.96)	0.16(1.28)
Proportion of children with lung function below the 5th centile according to the GLI-Other equations^a (%)										
zFEV ₁ (GLI-O)	17.0%	3.9%	24.8%	29.6%	18.7%	17.7%	1.7%	15.2%	9.1%	20.1%
zFVC (GLI-O)	13.6%	2.7%	29.8%	43.0%	17.8%	20.7%	4.5%	20.5%	5.3%	24.4%
zFEV ₁ /FVC (GLI-O)	5.9%	9.7%	4.3%	1.9%	12.3%	16.3%	1.7%	5.2%	11.3%	7.6%

Data presented as Mean (SD) unless otherwise specified. Centres A = Bangalore; B = Delhi; C = Gujarat; D = Hyderabad; E = CHASE (London); F = DASH (London); G = Leicester City; H = LRC (Leicester); I = SLIC (London)

^aIf the reference equations are appropriate, 5% of a healthy population would be expected to fall at or below the 5th centile (LLN). When data from Centres D and G were excluded (non-proportional reduction in FEV₁ and FVC), group mean(SD) for zFEV₁ was -0.60(1.11) z-scores; zFVC: -0.47(1.38) and zFEV₁/FVC: -0.18(1.26), while proportion of children with lung function below the 5th centile according to GLI-Black equations were 16.2%, 16.3% and 10.5% respectively.

doi:10.1371/journal.pone.0154336.t006

impact of SEC on lung function from Indian-based studies (Model 2) iii) all remaining datasets with proportional reductions in FEV₁ and FVC (Model 3).

After extensive analyses, preliminary GLI-adjustments were derived for the three models (S3 Table). Details of these preliminary models and data fit are presented in the S1 File, section 2.1 to facilitate future investigation and validation by any researchers who are able to collect high quality data from healthy South-Asian children.

Discussion

In this study we collated spirometry data from 8,124 subjects from four Indian-based and five UK-based studies of South-Asian children. After adjustment for age, sex and height using the GLI equations for White Europeans, FEV₁ was, on average, 15% lower in South-Asian children, with similar results for FVC emphasising the need for an ethnic adjustment when interpreting spirometry results from such children. By contrast, proportional reductions in FEV₁ and FVC in the majority of datasets meant that the FEV₁/FVC ratio, which is commonly used in the diagnosis of airway obstruction, remained independent of ethnic group. Despite the smaller

Table 7. Spirometry data from Delhi (Centre B) and Leicester (Centre G) according to GLI-Other reference.

Centre	N	zFEV ₁	zFVC	zFEV ₁ /FVC	%≤LLN zFEV ₁	%≤LLN zFVC	%≤LLN zFEV ₁ /FVC	Adj LLN [‡] zFEV ₁	Adj LLN [‡] zFVC	Adj LLN [‡] zFEV ₁ /FVC
B	670	-0.10 (0.93)	0.15 (1.02)	-0.42 (1.00)	3.9%	2.7%	9.7%	-1.55	-1.48	-1.96
G	177	0.23 (1.00)	-0.01 (1.04)	0.50(1.02)	1.7%	4.5%	1.7%	-1.27	-1.60	-1.34

Data presented as Mean (SD) unless otherwise specified. Abbreviations: GLI-O: GLI-“Other” reference; LLN: Lower limit of normal (equates to ≤ -1.645 z-scores). If the reference equations are appropriate, 5% of a healthy population would be expected to fall at or below the 5th centile (LLN); Adj LLN: LLN adjusted for the actual 5th centile according to centre.

doi:10.1371/journal.pone.0154336.t007

lung volumes in relation to height observed across all datasets, there was marked variability between centres in the magnitude of both the mean offset from predicted values in White subjects (which ranged from 4–19%) and the between-subject variability (coefficient of variation). Although the existing ‘GLI-Other’ equation fitted data from North India reasonably well while the ‘Black’ ethnic adjustment provided a better approximation for most of the other South-Asian data than the ‘White equation’, the marked disparities between centres persisted, irrespective of which equation was applied.

These findings confirm previous observations by Aggarwal and colleagues who compared spirometry equations from different subsets of the Indian adult population and found that the three sets of equations (from North, South and West India) did not yield interchangeable results, suggesting that there may be considerable heterogeneity in predicted lung function in various Indian subgroups[31]. While several paediatric reference ranges for specific regions in India have been published, the applicability of these equations to other parts of India has yet to be tested.

Strengths and limitations

Results from this study represent the largest collation of spirometry data from South-Asian children. Data were subjected to sophisticated statistical modelling which has been shown to be highly effective for developing all-age, multi-ethnic reference ranges[3]. However, the current data were collected for various purposes under a wide range of conditions, using different instrumentation and quality control with marked variability in the extent to which potential determinants of lung function had been documented. Thus, despite growing awareness of the potential effects of severe poverty [8,32–34], only two of the Indian-based studies reported such details. Similarly, lack of routine documentation regarding birth weight and gestational age in many regions within India, meant that children born prematurely or of low birthweight, both of which can have long term effects on lung function, could not be excluded from such studies. Since this was an opportunistic study based on retrospective data collection, we had no access to information on the extent of migration between rural and urban areas within India, nor details regarding ethnic sub-groups within the South-Asian population from several studies. The population included in this study was predominantly of Indian-origin and the relatively small sample size within other groups such as Pakistani and Bangladeshi precluded any definitive conclusions regarding the extent to which lung function may vary between such groups.

How representative were the subjects recruited to this study?

The issue of which subjects to include in a reference population remains debateable[23,35]. We used an opportunistic approach by contacting authors who had recently submitted data from healthy South-Asian children to the GLI-initiative or who had published such data in the past 15 years, but did not attempt to collate data from South-Asian adults[5], this being beyond the remit of the current study.

All data collated were community based, with most studies specifically designed to recruit from a random sample of schools which catered to a wide range of socio-economic circumstances to ensure a representative sample. Although the Hyderabad data were collected before publication of modern standards for paediatric spirometry[14] which could have introduced some bias, as discussed below, this dataset was excluded when modelling the new GLI-adjustments, so will not have influenced our overall findings.

To assess how representative the data were, we also compared anthropometric data to the current Indian growth charts, derived from 18,666 children attending 10 affluent schools from five major geographical regions of India[29]. After adjusting for age and sex, anthropometric

data from all but three centres (A, B and D) were comparable, with mean(SD) values ~ 0 (1), suggesting that the socio-demographics of most subjects included in this study were representative of well-nourished South-Asian children throughout India and the UK. As previously reported from a study of Punjabi children[36], South-Asian children from Northern India (Centre B) were taller and heavier than those from other centres. Whereas both anthropometry and lung function were lower in children from semi-urban/rural areas when compared with their urban counterparts in centre A, height and weight z-scores remained significantly lower in subjects from Centre D (Hyderabad) despite excluding all data from subjects from middle/low SEC, potential reasons for which could not be ascertained retrospectively.

Variability between and within centres. One of the most striking findings in this study was the variation in mean lung function between different centres. While FEV₁ and FVC were on average 15% lower than that in White children of similar age and height, this difference ranged from 4–19% across the datasets. While mean differences of up to 0.5 z-scores ($\sim 5\%$) in lung function can occur by chance in small samples[37], this could not account for differences between some of the larger centres included in this study. Similarly, there were marked differences in within-centre, between-subject variability. While not necessarily a reason for exclusion per se, inclusion of datasets with markedly increased coefficient of variation when deriving reference equations may decrease their sensitivity to detect lung disease[38]. Review of the literature reveals a similar degree of heterogeneity within the South-Asian population[5,7,39], reasons for which need urgent elucidation if reliable reference ranges are to be developed.

Methodological issues. An important factor contributing to differences in both mean values between centres and scatter of results within-centres may relate to equipment used. One possible contributory explanation for differences between Centre G and other centres could be systematic overestimation by the spirometer despite daily calibration, since the relative differences in FEV₁ and FVC between South-Asian and White children in this study were similar to other reports. While all centres strived to achieve international ATS/ERS standards, the quality of data will inevitably be influenced by the training, expertise and experience of the technical staff. Unfortunately, the lack of stored flow-volume curves with which to assess quality of spirometry data from six of nine centres (Table 1) meant that there were no objective criteria to separate valid from invalid measurements unless data were physiologically impossible. In contrast to some studies wherein strict QC was precluded by the type of spirometer used[5], Centres A (Bangalore) and I (SLIC study) both used a modern ultrasonic device which stores all data. This enabled immediate inspection of flow-volume data at time of collection as well as subsequent over-read, both essential features when assessing children[7,40]. Following quality control, this equipment also allows automatic upload of results into a research database, precluding transcription errors that may occur during manual entry.

In the current study, mean zFEV₁/FVC from all but two centres approximated zero (Table 2). When studying healthy children, a relatively low FVC combined with a normal or high FEV₁/FVC ratio, especially if combined with a wide scatter of results, may reflect poor subject cooperation, rather than lung restriction[41,42]. Additional discrepancies will have been introduced in several studies by failure to record age to at least 1 decimal year (Fig 1), the importance of which for accurate prediction of lung function was emphasised recently[3].

Impact of socio-economic circumstances. The marked secular changes in both lung function and growth that have occurred within developing nations such as India over the past 50 years[43] may contribute to increased variability of results in South-Asians, especially if exposed to extreme social deprivation[7], but are less likely to explain discrepancies in studies undertaken in the UK[9,26]. Despite minimal impact of SEC on lung function in children living in the UK[9,11,44], we recently reported a potential threshold effect of poverty, with lung function being significantly lower in children residing in rural India than in their urban

counterparts[7], which is in keeping with previous evidence[8]. In an attempt to avoid either over-diagnosis of lung disease in otherwise healthy children with evidence of growth restriction or poorer living conditions, or under-diagnosis in well-nourished children, separate GLI-adjustment factors were derived for these groups.

Regional differences? The extent to which inclusion of various South-Asian subgroups contributed to both heterogeneity of lung function within studies and differences between centres is difficult to ascertain due to sample size and inconsistency in the way in which such details were recorded. Despite inevitable mixing, people from north India have different ancestry from those in the south[45,46] which impacts on both anthropometry and lung function, and which may account for the higher lung function for data collected in Delhi[47]. Consequently, a separate preliminary equation was derived for this dataset.

While it is customary to use stature as a proxy for lung volume, this approach does not adjust for frame size including leg length in relation to torso (i.e. sit/standing height ratio). We have not reported detailed anthropometry regarding sit/stand ratio or chest dimensions in this report, as so few studies have included such measures, and those that did found that they made a relatively small contribution to observed differences between White and South-Asian children[9,26]. Nevertheless, while absolute lung volumes adjusted for stature may differ between ethnic groups, there is strong evidence that among healthy individuals, such differences in FEV₁ and FVC are proportional, as observed in over 60 datasets submitted to the GLI-2012 [30], resulting in an FEV₁/FVC ratio that is relatively independent of ethnicity and body size [3,23]. Datasets with non-proportional reductions in FEV₁ and FVC based on the 'White equation' were excluded prior to deriving South-Asian GLI-adjustment factors since not only may an elevated FEV₁/FVC in health reflect difficulties in achieving a full exhalation, but such findings are contrary to the majority of data previously published or submitted to the GLI.

Clinical and practical implications

While this study has provided clear evidence of ethnic differences in spirometric lung function among South-Asian children, it must be emphasised that the proportionally smaller values of FEV₁ and FVC observed do not reflect intrinsic differences in the functionality of the respiratory system, as reflected by the consistency of the FEV₁/FVC ratio. While derivation of an ethnic GLI-adjustment would potentially be the most efficient and cost-effective way of accommodating those of South-Asian origin as has been done for those of Black-African origin, results from this study suggest that no single adjustment will currently fit all data collected from this group, since there appear to be complex factors contributing to the heterogeneity observed within the South-Asian population. While it may be possible to address some of these factors in future, for example by greater standardisation of equipment, methodology and quality control, whereas the contribution of others, such as extreme poverty, may diminish over time with improved living standards, there may be some intrinsic differences related to genetic ancestry, which need further investigation. Meanwhile, the clinical dilemma of which equations to choose when interpreting spirometry results from South-Asian children remains. Personal communication with the authors from the Indian based studies included in this initiative, revealed that within most clinical centres in India, technicians frequently rely on the unspecified and disparate reference values presented as default by the manufacturers, a practice not unknown even in the UK[1]. Under these circumstances, adoption of a common standard such as the GLI all-age equations which are already available in most commercial lung function equipment (<http://www.ers-education.org/guidelines/global-lung-function-initiative.aspx>) would be far preferable, even if this did entail a small offset. Results from the current study suggest that until an improved solution can be found, use of the GLI-Black equations for the

majority of South-Asian children, or the GLI-other equation for those originating from North India, could provide an interim solution. For any clinical centre with access to a sizeable population (ideally at least 300[37]) of healthy children, use of such equations could be validated and if necessary the lower limit of normal adjusted to the local population, as discussed above (Table 7; see also S1 File, section 2.1.1, S6 Table).

Given that such an approach will need updating in future, we have included three alternative equations in the S1 File, in the hopes that this might stimulate further research using high quality equipment and standardised protocols to investigate the potential impact that SEC, geographical location or ethnic sub-groups may impact anthropometry and lung function within the South-Asian. When attempting to derive any new adjustment for South Asians, there needs to be a balance between limited generalisability if equations are based on a few homogenous datasets collected under ideal circumstances (which may not be achievable during routine clinical assessments) versus the lack of discrimination that will occur if such equations are derived from extremely heterogeneous data.

Conclusions and Future Directions

Variations in both the mean level of lung function and the degree of within-subject variability meant that none of the existing GLI-ethnic adjustments provided an ideal fit for all the datasets examined in this study and also precluded derivation of a single new South-Asian paediatric GLI adjustment. Given the current wide variation in equations used to interpret lung function from South-Asian children, an alternative approach would be to express results from South-Asian children using either the 'GLI-Black' or 'GLI -Other' equations, depending on region of origin, both of which are widely available in current spirometers.

Further prospective data collection among South-Asians residing within the Indian sub-continent as well as those who have migrated, using standardised protocols over a wider age range, is required to explore the potential sources of variation observed, with regular updating if there is evidence of significant secular changes. When undertaking such studies, age should be recorded in decimal years and standardised anthropometry include assessments of sitting height. All lung function assessments need to be undertaken according to ATS/ERS guidelines [14], adapted for children where necessary[40] using equipment that allows prospective QC at time of data collection, storage of all data for subsequent independent over-read and automated export of results to avoid transcription errors. Furthermore, documentation of relevant past and current medical history, environmental exposures and SEC should be as standardised as much as possible to facilitate subsequent collation or sub-division of data, and clarification of potential sources of variability (S8 Table).

In conclusion, despite some progress being made, the challenges we faced in attempting to derive spirometry reference equations for South-Asian children are perhaps best summarised by the following quote from Earl C. Kelley, Professor of Secondary Education at Wayne University (1951)[48]:

"We have not succeeded in answering all our problems—indeed we sometimes feel we have not completely answered any of them. The answers we have found have only served to raise a whole set of new questions. In some ways we feel that we are as confused as ever, but we think we are confused on a higher level and about more important things. So this report does not purport to give final answers, or to claim that we now "know how to do it". We see more need for revision than ever. But we are doing better than we did. And this is a progress report, rendered with humility because of the unsolved problems we see now which we could not see before."

Supporting Information

S1 Fig. Amendment to Excel Sheet calculator for calculation of lung function z-scores based on preliminary GLI-adjustments (for Model 3b).

(PDF)

S2 Fig. Data fit of the GLI-adjustment for Centre B using the smoothing function, plotted against height.

(PDF)

S3 Fig. FVC z-scores based on Model 2 (GLI-adjustments for A₂₋₃ & C) according to centre.

(PDF)

S4 Fig. Distribution of lung function z-scores calculated using GLI-adjustment based on Model 3a.

(PDF)

S5 Fig. FVC z-scores calculated using Model 3a (GLI-adjustments for A₁, E, F, H & I) according to centre.

(PDF)

S6 Fig. FVC z-scores based on Model 3b (GLI-adjustments for A₁, H & I) according to centre.

(PDF)

S1 File. Supporting information.

(PDF)

S1 Table. Recruitment and exclusion criteria according to respective studies.

(PDF)

S2 Table. Comparison of anthropometry between children residing in the UK and in India.

(PDF)

S3 Table. Preliminary GLI-adjustments according to the various models.

(PDF)

S4 Table. Lung function results based on Model 1 GLI-coefficients derived from Centre B (Delhi).

(PDF)

S5 Table. Lung function results based on Model 2 GLI-coefficients derived from Centres A₂₋₃ & C.

(PDF)

S6 Table. Lung function results based on GLI-coefficients derived from Centres A₁(urban), E, F, H & I (Model 3a).

(PDF)

S7 Table. Lung function results based on Model 3b GLI-coefficients derived from Centres A₁, H and I

(PDF)

S8 Table. Data required for prospective data collection.

(PDF)

Acknowledgments

The SLIC study team acknowledges the support of the National Institute for Health Research (NIHR), through the Comprehensive Clinical Research Network and the NIHR Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London.

Author Contributions

Conceived and designed the experiments: S. Lum JS. Performed the experiments: S. Lum SS CB SKC RKC DC SH CEK KVVP PW. Analyzed the data: VB PQ AW. Contributed reagents/materials/analysis tools: S. Lum SS CB SKC RKC DC SH CEK KVVP PW. Wrote the paper: S. Lum PQ JS AW VB SS CB SKC RKC DC SH CEK KVVP PW S. Lee. Collated the data: S. Lum S. Lee. Interpreted the data: JS PQ S. Lum.

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